AMENDMENTS TO THE CLAIMS

1. **(Currently amended)** A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the ~~sense strand or~~ antisense strand is modified by the substitution of ~~at least one internal nucleotide~~ each uridine with a ~~modified nucleotide~~ 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA.

2. **(Canceled)**

3. **(Currently amended)** The siRNA of any one of claims 1, 19, 21, 22, 27, 85, 92, 103 and 104, ~~claim 1 or 2 which is sufficiently complementary to a target mRNA, said~~ wherein the target mRNA ~~specifying~~ specifies the amino acid sequence of a cellular protein.

4. **(Currently amended)** The siRNA of any one of claims 1, 19, 21, 22, 27, 85, 92, 103 and 104, ~~claim 1 or 2 which is sufficiently complementary to a target mRNA, said~~ wherein the target mRNA ~~specifying~~ specifies the amino acid sequence of a viral protein.

5-18. **(Canceled)**

19. **(Currently amended)** ~~The siRNA of claim 6, wherein the modified nucleotide is selected from the group consisting of 5-bromo-uridine, 5-iodo-uridine, 5-methyl-cytidine, ribo-thymidine, 2-aminopurine, 5-fluoro-cytidine, and 5-fluoro-uridine, 2,6-diaminopurine, 4-thio-uridine; and 5-amino-allyl-uridine~~ A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the antisense strand is modified by the substitution of each uridine with 5-bromo uridine, such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA.

20. **(Canceled)**

21. **(Currently amended)** ~~The modified siRNA of claim 20, wherein the backbone-modified nucleotide contains a phosphorothioate group~~ A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the antisense strand is modified by the substitution of each phosphodiester linkage with a phosphorothioate linkage, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA and wherein the sense strand is unmodified.

22. **(Currently amended)** ~~The modified siRNA of claim 20, wherein the backbone-modified nucleotide contains a phosphorothioate group and is present within the sense and antisense strands~~ A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the antisense strand and the sense strand are modified by the substitution of each phosphodiester linkage with a phosphorothioate linkage, such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA.

23-26. **(Canceled)**

27. **(Currently amended)** ~~The siRNA of any one of claims 1-4, wherein the antisense strand and target mRNA sequences comprise at least one mismatch~~ A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the antisense strand is complementary to the sense strand throughout the siRNA but for mismatched base pairs at the two 3' nucleotides, referencing the antisense strand.

28-32. **(Canceled)**

33. **(Currently amended)** The siRNA of any one of claims 1, 84 and 85 ~~1-4~~, which is between about ~~10~~ 15 and ~~50~~ 25 residues in length.

34. **(Currently amended)** The siRNA of any one of claims 19 and 91-94 ~~1-4~~, which is between about 15 and ~~45~~ 25 residues in length.

35. **(Currently amended)** The siRNA of ~~any one of claims~~ claim 21 or 22 ~~1-4~~, which is between about ~~20~~ 15 and ~~40~~ 25 residues in length.

36. **(Currently amended)** The siRNA of any one of claims 27 and 101-105 ~~1-4~~, which is between about ~~18~~ 15 and 25 residues in length.

37-38. **(Canceled)**

39. **(Currently amended)** A composition comprising the siRNA molecule of any one of claims 1, 19, 21, 22, 27, 85, 92, 103 and 104 ~~1-4~~ and a pharmaceutically acceptable carrier.

40. **(Withdrawn)** A method of activating target-specific RNA interference (RNAi) in a cell comprising introducing into said cell the siRNA of any one of the preceding claims, said siRNA being introduced in an amount sufficient for degradation of target mRNA to occur, thereby activating target-specific RNAi in the cell.

41. **(Withdrawn)** The method of claim 40, wherein the siRNA is introduced into the cell by contacting the cell with the siRNA.

42. **(Withdrawn)** The method of claim 41, wherein the siRNA is introduced into the cell by contacting the cell with a composition comprising the siRNA and a lipophillic carrier.

43. **(Withdrawn)** The method of claim 40, wherein the siRNA is introduced into the cell by transfecting or infecting the cell with a vector comprising nucleic acid sequences capable of producing the siRNA when transcribed in the cell.

44. **(Withdrawn)** The method of claim 40, wherein the siRNA is introduced into the cell by injecting into the cell a vector comprising nucleic acid sequences capable of producing the siRNA when transcribed in the cell.

45. **(Withdrawn)** The method of claim 44, wherein the vector comprises transgene nucleic acid sequences.

46. **(Withdrawn)** The method of any one of claims 40-45, wherein the target mRNA specifies the amino acid sequence of a protein involved or predicted to be involved in a human disease or disorder.

47. **(Withdrawn)** A cell obtained by the method of any one of claims 40-46.

48. **(Withdrawn)** The cell of claim 47 which is of mammalian origin.

49. **(Withdrawn)** The cell of claim 47 which is of murine origin.

50. **(Withdrawn)** The cell of claim 47 which is of human origin.

51. **(Withdrawn)** The cell of claim 47, which is an embryonic stem cell.

52. **(Withdrawn)** An organism derived from the cell of claim 51.

53. **(Withdrawn)** A method of activating target-specific RNA interference (RNAi) in an organism comprising administering to said organism the siRNA of any one of the preeceeding claims, said siRNA being administered in an amount sufficient for degradation of the target mRNA to occur, thereby activating target-specific RNAi in the organism.

54. **(Withdrawn)** The method of claim 53, wherein the siRNA is administered by an intravenous or intraperitoneal route.

55. **(Withdrawn)** The method of claim 53, wherein the target mRNA specifies the amino acid sequence of a protein involved or predicted to be involved in a human disease or disorder.

56. **(Withdrawn)** An organism obtained by the method of any one of claims 53-55.

57. **(Withdrawn)** The organism of claim 56 which is of mammalian origin.

58. **(Withdrawn)** The organism of claim 56 which is of murine origin.

59. **(Withdrawn)** The organism of claim 56 which is of human origin.

60. **(Withdrawn)** The organism of any one of claims 56-59, wherein the target mRNA specifies the amino acid sequence of a protein involved or predicted to be involved in a human disease or disorder.

61. **(Withdrawn)** The organism of any one of claims 56-59, wherein degradation of the target mRNA produces a loss-of-function phenotype.

62. **(Withdrawn)** The method of claims 40-45 and 53-55, wherein degradation of the target mRNA is such that the protein specified by said target mRNA is decreased by at least 10%.

63. **(Withdrawn)** A method of treating a disease or disorder associated with the activity of a protein specified by a target mRNA in a subject, comprising administering to said subject the siRNA of any one of the preceeding claims, said siRNA being administered in an amount sufficient for degradation of the target mRNA to occur, thereby treating the disease or disorder associated with the protein.

64-83. **(Canceled)**

Please add the following new claims:

84. **(New)** The siRNA of claim 1, wherein the sense strand is unmodified.

85. **(New)** A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the sense strand and antisense strand are modified by the substitution of each uridine with 2'-fluoro uridine and each cytidine with 2'-fluoro cytidine, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA.

86. **(New)** The siRNA of any one of claims 1, 84 and 85, wherein the antisense strand is further modified by the substitution of each adenosine located within 2 nucleotides upstream and 3 nucleotides downstream of the cleavage site referencing the antisense strand with a 2'-deoxy adenonise and the substitution of each guanosine located within 2 nucleotides upstream and 3 nucleotides downstream of the cleavage site referencing the antisense strand with a 2'-deoxy guanosine.

87. **(New)** The siRNA of any one of claims 1, 84 and 85, wherein the antisense strand is further modified by the substitution of each adenosine with a 2'-deoxy adenosine and the substitution of each guanosine with a 2'-deoxy guanosine.

88. **(New)** The siRNA of any one of claims 1, 84 and 85, wherein the antisense and sense strands are aligned such that the siRNA has 3' 2-nucleotide overhangs.

89. **(New)** The siRNA of claim 88, wherein the 2-nucleotide overhangs are dTdT overhangs.

90. **(New)** The siRNA of claim 88, wherein the 2-nucleotide overhangs are UU overhangs.

91. **(New)** The siRNA of claim 19, wherein the sense strand is unmodified.

92. (New) A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the antisense strand is modified by the substitution of each uridine with 5-iodo uridine, such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA.

93. (New) The siRNA of claim 92, wherein the sense strand is unmodified.

94. (New) The siRNA of claim 92, wherein each uridine of the sense strand is substituted with 2'-fluoro uridine and each cytidine of the sense strand is substituted with 2'-fluoro cytidine.

95. (New) The siRNA of any one of claims 19 and 91-94, wherein the antisense and sense strands are aligned such that the siRNA has 3' 2-nucleotide overhangs.

96. (New) The siRNA of claim 95, wherein the 2-nucleotide overhangs are dTdT overhangs.

97. (New) The siRNA of claim 95, wherein the 2-nucleotide overhangs are UU overhangs.

98. (New) The siRNA of claim 21 or 22, wherein the antisense and sense strands are aligned such that the siRNA has 3' 2-nucleotide overhangs.

99. (New) The siRNA of claim 98, wherein the 2-nucleotide overhangs are dTdT overhangs.

100. (New) The siRNA of claim 98, wherein the 2-nucleotide overhangs are UU overhangs.

101. **(New)** A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the antisense strand is modified by the substitution of each purine with a 2,6-diaminopurine, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA.

102. **(New)** The siRNA of claim 101, wherein the sense strand is unmodified.

103. **(New)** A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the siRNA is modified within the 5' half of the siRNA referencing the antisense strand and unmodified within the 3' half of the siRNA referencing the antisense strand, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA.

104. **(New)** The siRNA of claim 103, wherein the modifications comprise substitution of each adenosine with a 2'-deoxy adenosine, substitution of each guanosine with a 2'-deoxy guanosine, substitution of each uridine with 2'-fluoro uridine and substitution of each cytidine with 2'-fluoro cytidine in the antisense strand.

105. **(New)** The siRNA of claim 103, wherein the modifications are within 9-19 nucleotides from the 3' end of the antisense strand.

106. **(New)** The siRNA of any one of claims 27 and 101-105, wherein the antisense and sense strands are aligned such that the siRNA has 3' 2-nucleotide overhangs.

107. **(New)** The siRNA of claim 106, wherein the 2-nucleotide overhangs are dTdT overhangs.

108. **(New)** The siRNA of claim 106, wherein the 2-nucleotide overhangs are UU overhangs.